

What is claimed is:

SUB P27 1. A pharmaceutical composition comprising at least one oligonucleotide in an emulsion.

2. The pharmaceutical composition of claim 1 wherein said oligonucleotide is an antisense oligonucleotide.

3. The pharmaceutical composition of claim 1 wherein said oligonucleotide modulates expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses.

SUB P31 4. The pharmaceutical composition of claim 1 wherein said oligonucleotide is a ribozyme, a peptide nucleic acid, a molecular decoy, an external guide sequence or an aptamer.

5. The pharmaceutical composition of claim 1 wherein said emulsion is an oil-in-water emulsion, a water-in-oil emulsion, an oil-in-water-in-oil emulsion or a water-in-oil-in-water emulsion.

6. The pharmaceutical composition of claim 1 wherein said emulsion is a microemulsion.

SUB P41 7. The pharmaceutical composition of claim 6 wherein said microemulsion is an oil-in-water microemulsion, a water-in-oil microemulsion, an oil-in-water-in-oil microemulsion or a water-in-oil-in-water microemulsion.

8. The pharmaceutical composition of claim 1 further comprising at least one penetration enhancer.

9. The pharmaceutical composition of claim 8 wherein said penetration enhancer is a fatty acid.

10. The pharmaceutical composition of claim 9 wherein said fatty acid is selected from a group consisting of arachidonic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprates, monoolein, dilaurin, glyceryl 1-monocaprates, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of claim 8 wherein said penetration enhancer is a bile salt.

12. The pharmaceutical composition of claim 11 wherein said bile salt is selected from a group consisting of cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydrofusidate, sodium glycodihydrofusidate, polyoxyethylene-9-lauryl ether or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition of claim 8 wherein said penetration enhancer is a combination of at least one fatty acid and at least one bile salt.

14. The pharmaceutical composition of claim 8 wherein said penetration enhancer is a chelating agent.

15. The pharmaceutical composition of claim 14 wherein said chelating agent is selected from a group consisting of EDTA, citric acid, a salicyclate, a *N*-acyl derivative of collagen, laureth-9, an *N*-amino acyl derivative of a beta-diketone or a mixture thereof.

16. The pharmaceutical composition of claim 8 wherein said penetration enhancer is a surfactant.

17. The pharmaceutical composition of claim 16 wherein said surfactant is selected from a group consisting of sodium lauryl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether, a perfluorchemical emulsion or a mixture thereof.

18. The pharmaceutical composition of claim 8 wherein said penetration enhancer is selected from a group consisting of unsaturated cyclic ureas, 1-alkyl-alkanones, 1-alkenylazacyclo-alkanones, steroidal anti-inflammatory agents and mixture thereof.

19. The pharmaceutical composition of claim 1 further comprising at least one carrier compound.

20. The pharmaceutical composition of claim 19 wherein said carrier compound is selected from a group consisting of polyinosinic acid, dextran sulfate, polycytidic acid, lipofectin, cationic glycerol derivatives, polylysine and 4-acetamido-4'-isothiocyano-stilbene-2,2'-disulfonic acid.

21. A method of treating an animal comprising administering to said animal a therapeutically effective amount of a pharmaceutical composition according to claim 1.

22. The method of claim 21 wherein said administration is buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary or urethral.

23. The method of claim 22 wherein said administration is rectal.

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24. The method of claim 23 wherein said rectal administration is by means of an enema.

25. The method of claim 23 wherein said rectal administration is by means of a suppository.

26. The method of claim 25 wherein suppository includes cocoa butter or hydroxypropylmethylcellulose.

27. The method of claim 21 wherein said animal is known or suspected to suffer from ulcerative colitis.

28. The method of claim 21 wherein said animal is known or suspected to suffer from Chrohn's disease.

29. The method of claim 21 wherein said animal is known or suspected to suffer from inflammatory bowel disease.

30. The method of claim 21 wherein said animal is known or suspected to suffer from undue cellular proliferation.

31. A rectal enema comprising an oligonucleotide in a solution.

32. The rectal enema of claim 31 wherein said solution is a saline solution.

33. The rectal enema of claim 31 wherein said solution is a buffered solution.

34. A method of treating an animal comprising administering to said animal a therapeutically effective amount of the rectal enema of claim 31.

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35. The method of claim 34 wherein said animal is known or suspected to suffer from ulcerative colitis.

36. The method of claim 34 wherein said animal is known or suspected to suffer from Chrohn's disease.

37. The method of claim 34 wherein said animal is known or suspected to suffer from inflammatory bowel disease.

38. The method of claim 34 wherein said animal is known or suspected to suffer from undue cellular proliferation.

39. A rectal suppository comprising an oligonucleotide and an excipient.

40. The rectal suppository of claim 31 wherein said excipient comprises cocoa butter or hydroxypropylmethylcellulose.

41. A method of treating an animal comprising administering to said animal a therapeutically effective amount of the rectal suppository of claim 39.

42. The method of claim 41 wherein said animal is known or suspected to suffer from ulcerative colitis.

43. The method of claim 41 wherein said animal is known or suspected to suffer from Chrohn's disease.

44. The method of claim 41 wherein said animal is known or suspected to suffer from inflammatory bowel disease.

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45. The method of claim 41 wherein said animal is known or suspected to suffer from undue cellular proliferation.

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46. A pharmaceutical composition comprising an oligonucleotide in oral dosage form.

47. The pharmaceutical composition of claim 46 wherein at least one of said covalent linkages of said oligonucleotide is a modified covalent linkage.

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48. The pharmaceutical composition of claim 47 wherein said modified covalent linkage is selected from the group consisting of a phosphorothioate linkage, a phosphotriester linkage, a methyl phosphonate linkage, a methylene(methylimino) linkage, a morpholino linkage, an amide linkage, a polyamide linkage, a short chain alkyl intersugar linkage, a cycloalkyl intersugar linkage, a short chain heteroatomic intersugar linkage and a heterocyclic intersugar linkage.

49. The pharmaceutical composition of claim 46 wherein at least one of the nucleotides of said oligonucleotide has a modified sugar moiety.

50. The pharmaceutical composition of claim 49 wherein said modified sugar moiety has a substitution or addition at the 2' position of a moiety selected from the group consisting of -OH, -SH, -SCH₃, -F, -OCN, -OCH₃OCH₃, -OCH₃O(CH₂)_nCH₃, -O(CH₂)_nNH₂ or -O(CH₂)_nCH₃ where n is from 1 to about 10, a C₁ to C₁₀ lower alkyl group, an alkoxyalkoxy group, a substituted lower alkyl group, a substituted alkaryl group, a substituted aralkyl group, -Cl, -Br, -CN, -CF₃, -OCF₃, an -O-alkyl group, an -S-alkyl group, an N-alkyl group, an O-alkenyl group, an S-alkenyl group, an N-alkenyl group, -SOCH₃, -SO₂CH₃, -ONO₂, -NO₂, -N₃, -NH₂, a heterocycloalkyl group, a heterocycloalkaryl group, an

aminoalkylamino group, a polyalkylamino group, a substituted silyl group, an RNA cleaving group, a reporter group, a DNA intercalating group, a group for improving the pharmacokinetic properties of an oligonucleotide, a group for improving the pharmacodynamic properties of an oligonucleotide, a methoxyethoxy group and a methoxy group.

51. The pharmaceutical composition of claim 46 wherein at least one of the nucleotides of said oligonucleotide has a modified nucleobase.

52. The pharmaceutical composition of claim 46 wherein said oral dosage form is selected from the group consisting of tablets, capsules and gel capsules.

53. The pharmaceutical composition of claim 46 wherein said oligonucleotide is an antisense oligonucleotide.

54. The pharmaceutical composition of claim 46 wherein said oligonucleotide modulates expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses.

55. The pharmaceutical composition of claim 46 wherein said nucleic acid is a ribozyme, a peptide nucleic acid, an external guide sequence, a molecular decoy or an aptamer.

56. The pharmaceutical composition of claim 46 further comprising an enteric material that substantially prevents dissolution of said tablets, capsules or gel capsules in a mammalian stomach.

57. The pharmaceutical composition of claim 56 wherein said enteric material is a coating.

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58. The pharmaceutical composition of claim 57 wherein said enteric coating is acetate phthalate, propylene glycol, sorbitan monoleate, cellulose acetate trimellitate, hydroxy propyl methyl cellulose phthalate or cellulose acetate phthalate.

59. The pharmaceutical composition of claim 46 further comprising a penetration enhancer.

60. The pharmaceutical composition of claim 59 wherein said penetration enhancer is selected from the group consisting of bile salts and fatty acids.

61. The pharmaceutical composition of claim 60 wherein said bile salt is selected from ursodeoxycholic acid, chenodeoxycholic acid, and salts thereof.

62. The pharmaceutical composition of claim 60 wherein said fatty acids are selected from capric acid, lauric acid, and salts thereof.

63. The pharmaceutical composition of claim 46 further comprising an excipient.

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64. The pharmaceutical composition of claim 63 wherein said excipient is selected from the group consisting of polyethyleneglycol and precirol.

65. The pharmaceutical composition of claim 46 further comprising a plasticizer.

66. The pharmaceutical composition of claim 65 wherein said plasticizer is diethyl phthalate, triacetin, dibutyl sebacate, dibutyl phthalate or triethyl citrate.

67. A method of treating an animal comprising administering to said animal a therapeutically effective amount of the pharmaceutical composition of claim 46.

68. The method of claim 67 wherein said animal is known or suspected to suffer from ulcerative colitis.

69. The method of claim 67 wherein said animal is known or suspected to suffer from Chrohn's disease.

70. The method of claim 67 wherein said animal is known or suspected to suffer from inflammatory bowel disease.

71. The method of claim 67 wherein said animal is known or suspected to suffer from undue cellular proliferation.

72. A method of modulating the expression of a gene in an animal comprising administering to said animal the pharmaceutical composition of claim 1.

73. A method of modulating the expression of a gene in an animal comprising administering to said animal the rectal enema of claim 31.

74. A method of modulating the expression of a gene in an animal comprising administering to said animal the rectal suppository of claim 39.

75. A method of modulating the expression of a gene in an animal comprising administering to said animal the pharmaceutical composition of claim 46.

76. A composition for oral administration comprising an oligonucleotide and a carrier wherein said oligonucleotide is conjugated to folic acid.

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77. The composition according to claim 76 wherein the folic acid is conjugated to the 5' terminus of said oligonucleotide.

78. The composition according to claim 77 further comprising an enteric substance resistant to degradation by gastric acids.

79. A method for introducing an intact oligonucleotide into a mammal, the method comprising the step of orally administering an oligonucleotide, wherein said oligonucleotide comprises a folic acid conjugated thereto.

80. The pharmaceutical composition according to claim 1, wherein said oligonucleotide is selected from the group consisting of ISIS-2302, ISIS-15839, ISIS-1939, ISIS-2922, ISIS-13312, ISIS-3521, ISIS-9605, ISIS-9606, ISIS-14859, ISIS-2503, ISIS-5132, ISIS-14803, ISIS-28089, ISIS-104838 and ISIS-2105.

81. The rectal enema according to claim 31, wherein said oligonucleotide is selected from the group consisting of ISIS-2302, ISIS-15839, ISIS-1939, ISIS-2922, ISIS-13312, ISIS-3521, ISIS-9605, ISIS-9606, ISIS-14859, ISIS-2503, ISIS-5132, ISIS-14803, ISIS-28089, ISIS-104838 and ISIS-2105.

82. The rectal suppository according to claim 39, wherein said oligonucleotide is selected from the group consisting of ISIS-2302, ISIS-15839, ISIS-1939, ISIS-2922, ISIS-13312, ISIS-3521, ISIS-9605, ISIS-9606, ISIS-14859, ISIS-2503, ISIS-5132, ISIS-14803, ISIS-28089, ISIS-104838 and ISIS-2105.

83. The pharmaceutical composition according to claim 46, wherein said oligonucleotide is selected from the

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group consisting of ISIS-2302, ISIS-15839, ISIS-1939, ISIS-2922, ISIS-13312, ISIS-3521, ISIS-9605, ISIS-9606, ISIS-14859, ISIS-2503, ISIS-5132, ISIS-14803, ISIS-28089, ISIS-104838 and ISIS-2105.

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